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PNEUMOCOCCUS MENINGITIS IN INFANTS AND CHILDREN

A Report on the Use of Combined Sulfonamides and Penicillin Therapy*

Sidney Ross, Lt. (j.g), (MC) USNR
Frederic G. Burke, M.D.

Introduction

Prior to the advent of chemotherapy and penicillin, few recoveries from pneumococcus menigitis were reported in the pediatric literature. Waring and Smith [1] reviewed 150 cases with a 100% mortality while Toomey and Roach [2] reported 157 cases with no recoveries. In Children's Hospital, Washington, D. C. there were 66 cases between 1923 and 1939 reported by Lindsay, Rice and Selinger [3] and Grossman [4] and of this entire series there was only one recovery. Other reports have been similarly discouraging.

The use of sulfonamide drugs represented a considerable advance in the therapy of pneumococcus meningitis over that previously used. However, the overall mortality even with the use of sulfonamide drug and type specific antiserum still ranged between 58% to 70% from 1940 to March, 1944 both in our series and in those reported from other institutions including the report of Hodes et al[5] from the Harriet Lane Hospital. In this regard, Dowling[6] in a review of the results obtained at Gallinger Hospital, Washington, D. C. from 1938 to 1941, reported only 4 recoveries in 7 cases. All these cases received sulfonamides and many received additional specific anti-serum. This indicated that prior to the advent of penicillin the mortality in pneumococcus meningitis was still inordinately high especially in infants and young children.

In April, 1944, a specific regime of therapy was adopted for pneumococcus meningitis at Children's Hospital consisting of combined sulfadiazine and penicillin which was to be initiated as soon as the diagnosis was made. The object of the remainder of this paper is to detail the results obtained in 19 consecutive cases with this regime since its inception and in addition to compare the results with those of previous modes of therapy in the 64 cases seen at Children's Hospital since 1940.

* Summary of a report which appeared in the Journal of Pediatrics, **29:** 677 (Dec.) 1946.

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Therapy

a. *Penicillin*

As soon as cloudy spinal fluid was encountered, 5,000 or 10,000 units of penicillin was instilled intrathecally. The penicillin was diluted in distilled water or saline so that 1,000 units equalled 1 cc. and an excess of spinal fluid was withdrawn prior to intrathecal instillation. Rammelkamp and Keefer[7] have shown in adults that such a dose of penicillin intrathecally is non-irritating and will remain in therapeutic concentration in the spinal fluid from 24 to 31 hours. Our own studies in infants and children concur with this observation. In 2 of the cases in the present series, an increase in the number of cells in the spinal fluid was noted in the fluid withdrawn after the second lumbar puncture. This increase in pleocytosis has been known to result occasionally after intraspinal injection of penicillin due to meningeal irritation. Penicillin given intrathecally should be introduced very slowly either by syringe or preferably by gravity in order to avoid any untoward central nervous sytem damage such as possible transverse myelitis. After intraspinal injection into the lumbar space, penicillin readily diffuses up into the ventricals, the cerebral and subarachnoid space, and over the convexities of the cerebral cortex in the absence of blockage. Rammelkamp and Keefer[7] reported the presence of a therapeutic titer of penicillin in the spinal fluid within the skull after lumbar intrathecal instillation. Clinically no untoward effects were noted from repeated intraspinal injections of penicillin in the present series. It is necessary to maintain careful asepsis in performing this procedure and to change the site of injection frequently in the lumbar region. The advantage of the intrathecal administration of penicillin in pneumococcus meningitis is derived from the fact that a very high concentration can be maintained at the site of infection. In none of the 19 cases was it necessary to administer penicillin into the cisterna magna or directly into the ventricular space; this latter procedure has been recommended by some authors but the dangers, except in the most experienced hands, would preclude its widespread use. Cairns[8] recently reported a case of palsy and dysphagia following intraventricular administration of penicillin. Another contraindication to the intraventricular route is that burr holes would be necessary in children whose fontanelle had already closed. Any block present in the foramina of Lushka or Magendie or the subarachnoid space would render valueless the intracisternal mode of administration. In our experience, the lumbar subarachnoid space is the preferred site of intrathecal injection and was used repeatedly in this series. Penicillin was administered by the intrathecal route usually on a daily schedule. The numbers of instillations ranged from 1 to 20 with an average of 6

injections for each patient. An individual dose of 5,000 units was routinely employed in all but 3 instances while the total intraspinal dose of penicillin ranged between 10,000 and 100,000 units, averaging approximately 30,000 units per patient. It was considered expedient to continue the intrathecal administration of penicillin until the spinal fluid had been sterile for 4 to 6 days.

Simultaneously penicillin was administered intramuscularly on a 2 to 3 hour schedule. With the exception of 2 patients, both of whom died within 6 hours after entry, the total amount of penicillin given intramuscularly in this series ranged between 300,000 units and 14,600,000 units, with an average of 2,800,000 units per patient. This amount was administered over the course of 4 to 30 days, an average of 16 days for each patient. It was customary to continue intramuscular penicillin therapy for at least a week and preferably 10 days after the temperature had returned to normal. As to the individual dose, it has been our experience that in order to achieve a good therapeutic concentration of penicillin in infants and children, it is desirable to give larger doses than one would expect on a weight for weight basis. Therefore, 10,000 to 30,000 units every 2 to 3 hours was administered even to the infant age group.

b. *Sulfonamides*

In the treatment of pneumococcus meningitis, in addition to penicillin, sulfonamides should be given in relatively large does. Toward this end, it has been our practice to use approximately 2 to 3 grains per pound of body weight subcutaneously in view of the fact that many of the patients are dehydrated and oliguric on entry due to vomiting or inanition. The avoidance of the intravenous administration of sulfonamide drug initially diminishes to a considerable degree the instances of hematuria resulting from crystallization of the drug in the kidney when oliguria is present. Once having initiated a good urinary output, the dangers from hematuria are considerably less. The immediate infusion of crystalloid fluids such as 1/6 molar lactate or 5% glucose in Hartmann's solution has the additional virtue of alkalinizing the urine and initiating the homeostatic acid-base regulatory mechanism of the kidney which is deficient in instances of oliguria and dehydration. No appreciable or significant delay is entailed in achieving an adequate blood-sulfonamide level when the subcutaneous mode of administration is employed rather than the intravenous route. Adequate levels of sulfonamide drug were usually considered to be in the range of 12-20 mgms. % in our cases of pneumococcus meningitis; this was readily achieved by the administration of approximately 2 to 3 grains per pound of body weight in 24 hours given by hypodermoclysis divided into 8 hour doses. Sulfonamide drug given parenterally as the sodium

salt is administered either in 1/6 molar lactate, 5% glucose in Hartmann's solution or normal saline, as a 1% solution which is non-irritating under the skin. The parenteral mode of administration of sulfonamides was maintained until the patient was able to retain the drug orally. In infants where difficulty may be encountered in administering sulfadiazine in the powdered form by mouth, we have recently used sodium sulfadiazine (in 5% solution) orally and the infants seemed to tolerate it well and received the entire dose intended.

Four cases in this series developed hematuria within the first 2 to 4 days. However, in view of the urgency of maintaining the sulfonamide drug, it was thought inadvisable to discontinue the drug at that time. Fluids were forced intravenously, by clysis and by mouth. Bicarbonate of soda was administered and the dosage of sulfadiazine was reduced to 1 to 1½ grains per pound of body weight. In each instance, the hematuria cleared up without any untoward complications. It would seem that hematuria per se does not constitute a cogent reason for discontinuing sulfonamide drug in cases of pneumococcus meningitis in view of the fact that discontinuing the drug prematurely may have an untoward effect on the course of the disease. However, each case has to be individualized. In some instances when hematuria develops, it may be possible to discontinue the drug with impunity especially when the child is convalescent or the infection is mild. Anuria is a more definite indication for discontinuing sulfonamide therapy than hematuria. Crystalluria is a frequent finding in cases where sulfonamides are used in large doses, but does not seem to be of any real significance and certainly does not constitute an indication for discontinuing the drug. During the acute phase of the infection, it may be deemed advisable to risk the more remote possibility of kidney damage rather than fail to maintain a full measure of therapy against pneumococcus meningitis. In this series, sulfadiazine was maintained for approximately 8 to 12 days after the temperature had returned to normal.

c. *Type Specific Antiserum*

In the present series where combined sulfonamide and penicillin therapy was employed, type specific antiserum was administered only in the first seven consecutive cases while it was routinely omitted in the next 12 cases. In the 7 cases receiving type specific antiserum in conjunction with sulfonamide drug and penicillin there were 6 recoveries and one death. Four of these 7 cases were in the infant age group (one year and under). In the 12 cases where the antiserum was omitted, there were 10 recoveries and 2 deaths; however, as will be described later, both these fatalities occurred within 6 hours after hospital admission. Seven of these 12 cases were infants. The average severity of the infection at the time of entry was

roughly comparable in both those who received type specific antiserum and in those in whom it was omitted; the element of selection was therefore probably minimal. There appeared to be no perceptible difference in the course or morbidity in the cases where serum was not used. Because this series is small it is difficult to appraise the value of serum as an adjunct in therapy when combined sulfonamide-penicillin is employed. It is probable that combined therapy may have minimized the need for type specific antiserum. Our results would indicate that is is safe to omit antiserum at the beginning of therapy and allow its necessity to be determined by the course of the infection.

d. *Supportive Therapy*

Supportive measures are also indicated including adequate amounts of fluid to combat dehydration, amino acid preparations and plasma to repair protein deficit, as well as whole blood. These all have distinct value. The majority of the cases in the present series received at least one whole blood transfusion during the course of their illness.

e. *Heparin and Spinal Fluid Drainage*

In 5 of the patients where it appeared that a chronic basilar meningitis was developing as indicated by varying degrees of spasticity and a viscid spinal fluid with elevated protein, it was deemed advisable to instill heparin intrathecally (1 cc. per dose) for 3 or 4 consecutive days. Simultaneously spinal fluid drainage was attempted with the substitution of air into the subarachnoid space. This was thought to have the virtue of breaking up any small adhesions that might have formed and in maintaining free flow between the ventricles and the spinal subarachnoid space. In one instance, heparin was discontinued after xanthochromic fluid was obtained, this occurring after 40 mgms. or 4 cc. of heparin had been injected intrathecally over the course of 4 days. It is impossible to evaluate accurately the role of intrathecal instillation of heparin in this small series. Alexander[9] has used heparin in 2 cases of H. influenza meningitis and Friedman and Signorelli[10] in one patient and reported some benefit from its use. In the 9 cases of pneumococcus and H. influenza meningitis which received heparin and air intrathecally during the past year at Children's Hospital, it seemed that some improvement did follow its use. Purely on an empirical basis, it would appear advisable to employ the intrathecal injection of heparin and air as a last resort in those instances where development of chronic basilar meningitis is suspected. This is especially important in cases where therapy has been instituted late and where infection has had ample time to produce walled-off pus pockets.

f. *Follow-up Laboratory Work*

Daily sulfonamide levels should be obtained during the first week and for the sake of uniformity, it is desirable to obtain the assay about one hour before the next dose is to be administered. The blood levels in this series were maintained between 12 and 20 mgm. %. A daily urinalysis should be performed to watch for toxic drug effects, especially hematuria. Daily spinal fluid examinations during the acute phase of the disease were singularly helpful in permitting a rather objective evaluation of the patient's course. A decrease in the cell count and protein and an increase in the sugar content can often be construed as favorable prognostic indications. In the series of 19 cases treated with combined penicillin-sulfonamide therapy, spinal fluid cultures became negative on an average of 3 days after initiation of treatment. However, no penicillinase was added to these spinal fluid cultures and it may well have represented in part an inhibition of the culture growth of the organism by the penicillin already present in the spinal fluid.

It cannot be stressed to strongly that both sulfonamides and penicillin should be continued for at least 8 to 12 days after the spinal fluid has become sterile.

g. *Surgical Intervention*

As previously noted, otitis media was a frequent associated finding in this series. Resort to the judicious use of surgery in cases of complicating mastoiditis and other foci amenable to surgery is usually regarded as a therapeutic adjunct of primary importance. However, in the current series where combined sulfonamide-penicillin therapy was employed, no mastoidectomies were performed. It is still speculative whether or not our current therapy makes surgical intervention less imperative.

Results

In 19 consecutive cases of pneumococcus meningitis treated with combined sulfadiazine and penicillin, there were 3 deaths.

The first fatality occurred in a one year old infant who was admitted in April, 1944 when penicillin was still relatively unavailable. He received sulfadiazine, type specific antiserum and supportive therapy for the first 6 days after admission and only when his condition appeared to have become critical was penicillin instituted more or less as a terminal measure. The dose was 5,000 units every three hours and he received a total of 60,000 units. The infant died on the 8th hospital day, 2 days after the initiation of penicillin therapy. No intrathecal penicillin was administered.

The second death occurred in a 12 year old boy who was admitted to the hospital in a moribund condition after having received a skull fracture

involving the anterior fossa and the cribiform plate with complicating pneumococcic meningitis. The child, prior to entry, had received ¼ grain of morphine which might have been contributory to his rapid exitus. He remained stuporous and died 6 hours after admission. One dose of penicillin intramuscularly (50,000 units) and one dose of sodium sulfadiazine was administered prior to death.

The third death was that of a 9 year old girl who was comatose at the time of hospital entry and had a temperature of 106°. She received one intrathecal dose of penicillin (10,000 units) and 2 intramuscular injections of 40,000 units at 2 hour intervals; in addition, one parenteral dose of sodium sulfadiazine was administered. However, the child never regained consciousness and died 6 hours after admission.

Thus in 2 of the 3 fatalities death occurred within 6 hours after admission to the hospital; the rapid terminal progression was such that it precluded

AGE	NO. OF CASES	RECOVERIES	% RECOVERIES
Less than 6 mos.	7	7	100%
6–12 mos.	2	2	100%
1–2 years	5	4	80%
2–6 years	1	1	100%
6–12 years	4	2	50%
	19	16	

CHART 1. RECOVERIES BY AGE IN 19 CASES OF PNEUMOCOCCUS MENINGITIS TREATED WITH COMBINED SULFONAMIDE DRUGS AND PENICILLIN

Seven of the 19 cases received type specific antiserum in addition

an evaluation of the efficacy of combined therapy in both cases. A fair trial of therapy would require a survival of at least 12 to 24 hours after its initiation before its effect could be ascertained.

In the 16 remaining cases, it was considered that adequate combined sulfonamide drug and penicillin had been employed and in every case recovery ensued.

It is of some interest to note the age distribution as related to the incidence of recoveries (Chart 1). Nine of the 19 cases were under one year of age; of these, there were 7 cases under 6 months while the other 2 ranged from 6 to 12 months. These 9 infants all recovered in spite of the fact that the duration of illness in the infant group prior to the initiation of combined therapy ranged from 2 to 8 days with an average of 3 days per patient. This assumes a degree of importance when the usually high mortality rate attendant to this age group is considered. The reason for the hitherto high mortality in infants under one year has been variously attributed to

a poorer antigenic response and/or greater susceptibility to pneumococcal infections. No less important, however, is the frequent delay in making an early diagnosis in infants because of the paucity of physical findings during that stage of the disease when it is more amenable to therapy.

The conclusion seems warranted that if all the adjuncts in therapy previously outlined are brought to bear as quickly and as vigorously as possible, the prognosis, even in the infant age group, is relatively good.

The youngest patient in this series was a six week old colored male whose course in the hospital was as follows:

The infant was admitted with a history of fever and diarrhea of 6 days duration. Several episodes of vomiting and drowsiness occurred 4 days prior to entry. At the time of admission, the infant was critically ill with marked spasticity, partial opisthotonos and coarse persistent tremors were noted. The temperature was 104°. Spinal tap yielded cloudy fluid containing 610 white cells with 93% polymorphs; sugar was absent and protein content was 60 mgm. %. Pneumococcus (type 8) was found on smears and culture.

The child received sulfadiazine parenterally (2 to 4 grains per pound body weight) and penicillin, both intramuscularly and intrathecally. The intramuscular dose ranged between 30,000 to 50,000 every 2 hours, and a total dose of 14,600,000 units was administered over the course of 4½ weeks during which penicillin therapy was maintained. The intrathecal dose of penicillin was 5,000 units daily and 16 intrathecal injections were administered for a total of 80,000 units. In addition, 1 cc. of heparin intrathecally was given on 4 consecutive days when it became apparent that a chronic basilar meningitis was developing. Supportive therapy included parenteral fluids, blood transfusions, oxygen and sedation for persisting convulsions. No type specific pneumococcus antiserum was used.

A stormy course in the hospital ensued punctuated by a complicating urinary tract infection (due to B. coli) and persisting diarrhea. The opisthotonus and spasticity gradually disappeared and after the first week, no further convulsive seizures were noted. The spinal fluid became sterile within 5 days after admission and remained so during the remainder of the hospital course. The infant was discharged ostensibly well after a 6 week hospital stay. The matter of residual central nervous system damage will have to be determined by future follow-ups.

A comparison of the recoveries from pneumococcus meningitis in children under 2 years of age is made with those reported from other institutions (Chart 2); it would seem that the percentage of recoveries appears to be directly proportional to the incidence of the use of combined penicillin and sulfonamide treatment; the less favorable results appear to have been obtained when penicillin was used alone. This is in keeping with War-

ing and Smith's conclusion[1] that penicillin alone seemed capable of curing the disease only in a relatively small percentage of cases; in other cases, it was able to check the course of the disease for a limited period but was unable to arrest it completely. It is difficult to say whether peni-

AUTHORS	NUMBER OF CASES	COMBINED PENICILLIN AND SULFONAMIDE Rx	RECOVERY	DIED	% RECOVERY	RECOVERIES WITH RESIDUAL CNS DAMAGE
White et al.[11] ...	12	14% of total series received combined therapy	5	7	41.7%	4
Hutchins and Davies[12]	14	64%	9	5	64.4%	5
Waring and Smith[1]	9	92%	8	1	88.8%	3
Children's Hospital, Wash., D. C.	14	100%	13	1	92.9%	3

CHART 2. ANALYSIS OF PNEUMOCOCCUS MENINGITIS IN CHILDREN UNDER 2 YEARS OF AGE WITH A COMPARISON OF THE RESULTS REPORTED FROM VARIOUS INSTITUTIONS

Note the correlation between the incidence of recoveries and the number of cases where combined penicillin and sulfonamide drug were employed

THERAPY	TOTAL	RECOVERIES	DEATHS	% RECOVERIES
Non specific	16	0	16	0
Serum alone	6	0	6	0
Sulfonamide alone	21	2	19	9.5%
Sulfonamide and serum	33	10	23	33%
Sulfonamides and penicillin	12	10	2	83.3%
Sulfonamides, penicillin and serum	7	6	1	85.7%
	95	28	67	

CHART 3. A COMPARISON OF THE RESULTS OBTAINED WITH VARIOUS TYPES OF THERAPY IN 95 CASES OF PNEUMOCOCCIC MENINGITIS TREATED AT CHILDREN'S HOSPITAL SINCE 1933

cillin and sulfonamides, used in combination, act by summation or by synergistic action but, whatever the modus operandi, combined therapy is the treatment of choice in pneumococcus meningitis.

In this regard, it is of interest to compare the results obtained with the

various types of therapy indicated in Chart 3 in 95 cases of pneumococcus meningitis treated at Children's Hospital since 1933. The gratifying increase in recovery rate since the advent of chemotherapy and penicillin can be clearly noted.

In Chart 4, the recoveries from pneumococcal meningitis since 1940 are correlated with age and type of therapy. The 84.2% recovery rate with combined sulfonamide-penicillin therapy is in striking contrast to the 25.6% recovery rate obtained with sulfonamide drugs alone.

Complications

In this series, 3 of the 16 children who recovered had complications. One patient, a 6 year old boy (Case 2) had residual deafness, while another

Age	Sulfonamides			Sulfonamides and penicillin		
	Total	No. of recoveries	% recoveries	Total	No. of recoveries	% recoveries
Up to 1 year	31	6	19.4%	9	9	100%
1–2 years	5	1	20.0%	5	4	80%
3–12 years	7	4	57.1%	5	3	62.5%
	43	11	25.6%	19	16	84.2%

Chart 4. Recoveries Correlated with Age and Type of Therapy in 62 Cases of Pneumococcal Meningitis Since 1940

The advantage of combined sulfonamide-penicillin therapy over sulfonamide drug alone is evident. Note the 100% recovery rate in the infant age group when combined therapy was employed. The relatively low incidence of recovery in the 3 to 12 year age group is more apparent than real in view of the fact that the two deaths in this age group occurred within 6 hours after admission and did not constitute an adequate trial of the efficacy of combined therapy.

child, 14 months of age, was spastic and appeared to be blind at the time of discharge. A third child, age 3 months, suffered several relapses during his course in the hospital due probably to premature discontinuation of intrathecal penicillin. This patient received both heparin and air intrathecally when it became apparent that a chronic basilar meningitis had developed. A pneumonencephalogram revealed widely dilated lateral ventricles with evidence of moderately advanced hydrocephalus. The infant eventually recovered from his infection after a protracted course and was discharged with a guarded prognosis. However, when seen on follow-up examination several months later, he had shown remarkable improvement in his mental and physical performance. This serves to emphasize the importance of follow-up studies on infants, who, following meningitis, had shown evidence of incipient hydrocephalus and spasticity.

Some of these patients with residual central nervous system damage show considerable improvement in spite of the poor prognosis which is usually entertained at the time of discharge from the hospital. As Hartmann[13] points out, hydrocephalus following meningitis may be transient in some cases owing to the failure of absorption of spinal fluid over the cortex because of inflamed meninges, with subsequent regression of the dilatation of ventricles as absorption approaches normal.

It is to be noted that 2 of the 3 patients with complications in this series were ill for 8 days before the diagnosis was made and treatment instituted. This serves to re-emphasize the importance of early diagnosis if full recovery without central nervous system sequellae is to be expected.

It is well known that pneumococcus meningitis characteristically produces a viscid exudate consisting of fibrin and pus over the entire brain surface and may readily produce an adhesive arachnoiditis involving the foramina of Lushka and Magendie. This may act as a focus for relapse and the puspockets formed may prevent the penicillin from coming in intimate contact with the organisms. The only adequate way of preventing this unfortunate complication is to begin vigorous treatment before the formation of this thick plastic exudate.

In any case where meningitis is suspected, the practice of having a bottle of penicillin available at the bedside at the time of the initial lumbar puncture has been adopted at Children's Hospital. In the event the spinal tap yields turbid fluid, penicillin is immediately instilled intraspinally before the nature of the organism is determined. This is based on the premise that it is more important to institute prompt and vigorous therapy in meningitis in view of its gravity than to await a bacteriologic diagnosis before initiating therapy. There are no clinical signs which enable one to distinguish one type of pyogenic meningitis from another clinically except for the presence of petechiae in the meningococcus type. In addition it occasionally happens that because of excessive decolorization or poor staining, pneumococcus may be mistaken for meningococcus and vice versa. Also in those cases where H. influenza organisms are present in very small numbers with the predominance of coccal forms, there is the possibility of confusing these forms with either pneumococcus or meningococcus. Intrathecal administration of penicillin is indicated in all types of coccal meningitis and the only instance where its use would be without special value is H. influenzal meningitis. The important consideration, however, is that vigorous therapy has been instituted quickly if the organism turns out to be either pneumococcus or meningococcus. We have all experienced instances where the stained smear was equivocal as to the etiological organism, and where it was necessary to await the results of culture which would not be forthcoming for 24 to 48 hours. Such a delay

would contribute to a less favorable prognosis since the outcome in meningitis is in no small part predicated on the rapidity with which adequate therapy is instituted.

Conclusions

1. Nineteen cases of Pneumococcus Meningitis in infants and children were treated with combined sulfonamide and penicillin therapy. Of this number 16 cases recovered and 3 died. Two of the deaths occurred within 6 hours after entry. Three of the cases which recovered showed residual central nervous system sequellae.

2. Excretion studies performed on infants and children indicate that penicillin should be administered both intramuscularly and intrathecally to achieve therapeutic spinal fluid penicillin concentrations in meningitis.

3. Sulfadiazine was used in conjunction with penicillin in the present series. The combination of both drugs appears to offer definite advantages over penicillin alone. Therapy should be continued for at least 8 to 12 days after sterilization of the spinal fluid.

4. Of the 19 cases receiving combined sulfonamide-penicillin therapy, type specific antiserum was administered only in the first 7 consecutive cases while it was routinely omitted in the next 12 cases. Of the 7 cases receiving antiserum, there were 6 recoveries and one death, while in the 12 cases where antiserum was omitted, there were 10 recoveries and 2 deaths. Because the series is small, it is difficult to appraise the value of antiserum as an adjunct in current therapy. It is probable that combined sulfonamide-penicillin treatment may have minimized the need for type specific antiserum.

5. Heparin was administered intraspinally in cases where chronic basilar meningitis developed and was thought to have some value in the treatment of this complication.

6. The importance of the early institution of therapy in pneumococcus meningitis cannot be over-emphasized. If all the adjuncts in present day therapy are brought to bear as quickly and as vigorously as possible, the prognosis, even in the infant age group, is relatively good.

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CONGENITAL HEMOLYTIC ANEMIA

Case Report No. 81

John Nestor, M.D. J. L. 46–1604

J. L., a 3 year old white girl, was admitted to Children's Hospital on March 4, 1946 with a chief complaint of jaundice, vomiting, abdominal pain, and a head cold. The patient had attended the clinic at Gallinger Hospital where, in December 1945, physical examination revealed a pale, thin, girl with a soft systolic murmur in the 2nd left interspace and a spleen palpable one finger breadth below the left costal margin. No jaundice was observed at this time. On March 3, 1946, the day before admission to Children's Hospital, the patient refused solid food and about 11:00 p.m. she began to vomit foul-smelling, orange-colored material. Jaundice was first noted the following morning, the day of admission. The stools were darker than normal and slightly looser than usual. She also seemed to bruise easily.

The past history revealed the child had been born prematurely at home after 7 months gestation and weighed 5 pounds; labor was easy, delivery spontaneous and a physician was in attendance. The baby was breast fed for 3 months and then given a formula of evaporated milk, boiled water and Karo. Orange juice was started at 1 month, cereal at 6 weeks, vegetables at 3 months. Cod liver oil was not started until the 8th month at which time the baby weighed only 9 pounds. Her first teeth appeared at 7 months; she talked at 18 months and walked at 26 months.

The father had luetic treatment for one year and a half prior to his marriage. He states all blood tests since then have been negative. Two sisters of the patient, ages 1 and 3 years, died of pneumonia within a week of each other. These 2 sisters were always pale and looked very much like the patient. There is no history of familial or hereditary disease and no evidence of jaundice, bleeding tendency, or anemia in any other member of the family.

Physical examination on admission revealed a fairly well developed, well nourished female, slightly underweight and markedly jaundiced. There was a nasal discharge, pale buccal mucosa, injected pharynx, and ear drums thickened and dull but not inflamed. The right cervical glands were palpable. The spleen was large, firm, non-tender, and was palpable 3 fingers below the left costal margin. The heart seemed to be enlarged somewhat to the left and there was a systolic murmur heard best at the apex but audible over the entire precordium. The laboratory work is summarized in the accompanying chart.

The hospital course was one of rapid and progressive improvement. Visible jaundice disappeared in 28 hours, the spleen rapidly diminished in size though the size varied considerably from day to day. The patient never showed clinical jaundice after the original crisis on admission. The patient developed measles while in the hospital and splenectomy was postponed until May 9, 1946, when it was performed without unusual difficulty. She was observed closely for two weeks following the operation and repeated blood work showed no marked or immediate change in the RBC or thrombocyte counts. On June 16, 1946 the child returned to the hospital for a complete check-up. Her father stated there was marked improvement in her general condition, that she ate much better, did not tire easily, and played more than formerly. Laboratory work at this time showed a hemoglobin of 13 grams with 3.76 million red blood cells; the white cell count and differential were within normal limits. Fragility test was normal with hemolysis ranging from .46% to .36% while the quantitative Van den Bergh showed .52 mgm % of bilinogen.

Discussion

Dr. Beldon Reap: The hemolytic anemias are usually divided into two groups, primary and secondary. The outstanding members of the primary group are hemolytic jaundice, sickle-cell anemia, Von Jaksch's anemia and paroxysmal hemoglobinuria. The secondary group are caused by malaria, snake venom, hemolytic streptococcal infection, and pernicious anemia.

Two clinical types of hemolytic anemia are recognized, congenital (Chauffard-Minkowski type) and acquired (Hayem-Widal type). The acquired type is probably an activation of a latent congenital type secondary to an acute infection. It differs from the familial type only in the late onset and the difficulty in tracing the hereditary background.

True congenital hemolytic anemia is both familial and congenital and it is due to an inherited anomaly of the erythrocytes, transmitted by either sex as a dominant Mendelian characteristic. It becomes increasingly severe with each successive generation, yet may avoid detection because of the mildness of the hemolytic process. When one parent only is affected, half the children will be carriers of the disease through generations. Occasionally it appears in several brothers or sisters although the parents are unaffected. At the same time it must be noted that the child may be the only member of the family to be affected. It frequently happens that although other members have apparently escaped, one or more of them may show the characteristic increased fragility of the red cells.

Clinical symptoms may develop at any age but the usual period is from early childhood to adolescence. The disease is characterized by a pecu-

LABORATORY TEST	LABORATORY EXAMINATIONS				
	1/11/46	3/4/46	3/5/46	3/6/46	3/8/46
Icterus Index	15	122.5		67.5	36
Van den Bergh (qualitative)		Immed. direct		Immed. direct	Delayed reaction
Van den Bergh (quantitative)		3.2 mgm./ 100 cc.		3.7 mgm./ 100 cc.	2.6 mgm./ 100 cc.
Hemoglobin	9.2 gms.	11.0 gms.			
Erythrocytes	2,780,000	3,240,000	(3,880,000—5/16/46 and 3,680,000 —5/23/46).		
Leukocytes	9,400	8,600			
Neutrophils	50%	60%			
Lymphocytes	49%	37%			
Eosinophils	—	2%			
Monocytes	1%	1%			
Thrombocytes	273,000	700,000	(300,000—5/16/46 and 400,000—5/23/46).		
Nucleated erythrocytes	None	Rare			
Spherocytes		Many—There was also marked polychromatophilia, achromia, and anisocytosis			
X-ray skull, long bones	Negative		Negative		
Reticulocytes			18%		
Kahn			Negative		
Cephalin flocculation				Negative	
Fragility of erythrocytes:					
Hemolysis began	0.72%		0.60%	0.70%	
Hemolysis complete	0.42%		0.42%	0.42%	

On March 4, 1946, the following tests were also made:
Prothrombin Time—15 sec. (122% of normal).
Bleeding Time—2 min. (Normal is 1 to 3 min.).
Coagulation Time—2 min. 10 sec. (Normal 5 to 8 min.—Lee-White).
Clot Retraction Time—W/N 2 hrs. (Normal 1 hr.).

CHART 1. SUMMARY OF LABORATORY RESULTS OBTAINED BEFORE SPLENECTOMY

liar type of red blood cell instead of the normal, flattened, biconcave disc. The thicker erythrocytes of decreased diameter rupture more readily in hypotonic solutions because of their loss of biconcavity. The fragility varies directly with the degree of spherocytosis. Normally a red cell assumes the spheroid form before hemolyzing in hypotonic salt solution and, since the cells are already spheroid, hemolysis becomes complete in much less hypotonic solution than cells of normal shape. Several factors influence the shape of the cell in this congenital disorder apart from the continued action of an hemolysis. Iron deficiency will flatten the spherocyte; Addisonian deficiency will enlarge the cell; infection will increase the sphericity. There is, therefore, no correlation between degree of spherocytosis and severity of the disease, onset of crisis, decrease in osmotic resistance, extent of anemia or rapidity of red cell regeneration. Indeed, cases of hemolytic jaundice occur in which the resistance of the cells is normal from birth, though their structure is defective. These abnormal cells are produced by the bone marrow because of a constitutional anomaly in the specific gene associated with a disturbance in cholesterol metabolism.

The cells formed are destroyed by the reticuloendothelial system within a few days instead of a few weeks, and rapidly removed from the circulation, leading to the development of an overactive and an enlarged spleen. There is, therefore, a compensatory increase in the output of these small erythrocytes from the bone marrow in an effort to maintain cellular equilibrium in the blood, resulting in a hyperactive marrow with hyperplasia of erythropoietic tissue. This equilibrium enables the child to function efficiently with red cells and hemoglobin maintained at relatively higher levels than would otherwise be possible.

Granulopoietic elements are also involved in the process; hence there is an associated granulocytic leukocytosis. When the demand on the marrow becomes excessive, nucleated red blood cells such as normoblasts, microblasts, and immature white blood cells are poured into the circulation. But such a circumstance produces a clinical attack with pronounced symptoms, especially from intercurrent infection or excessive activity. The child remains apparently well, depending on the rates of production and destruction of spheroid cells, and the marrow capacity to compensate for cellular loss. The disease becomes well defined when the functional capacity of the marrow fails in the mechanism of compensation.

Clinically, congenital hemolytic anemia exhibits two stages:—latent, and active. The disease may remain latent throughout life. The defective red cells may be noted in a routine blood examination; sometimes jaundice may be present, as may anemia. In the active stage, the acute attack may produce a hemolytic crisis due to the sudden liberation of large amounts of hemolysin, or be induced by emotional disturbance, ultra-

violet irradiation, infection or physical exertion, for the margin of safety against hemolysis of the red cell is very narrow. The onset is usually abrupt with fever and chills, rapid increase in icterus and plasma iron, marked fall in hemoglobin, red cells, white cells and platelets, enlargement of the spleen, abdominal pain associated with perisplenitis, and increased urobilin excretion in the stools and urine. The rate of blood destruction may vary, but once activity is established there is little tendency for the disease to return to the latent stage. The duration of the attack may be a few days to a few weeks. The intensity of the attack may be so mild as to be scarcely perceptible or so extreme as to cause great concern about the outcome. As the symptoms subside, there is an increase in blood regeneration with a rise in erythroblasts, platelets, leukocytes, and various early forms. Four types of hemolytic attacks occur in children: (1) *The Icteric type*, characterized by a feeling of lassitude followed by a high fever, sudden jaundice, enlargement of the liver and spleen, vertigo, breathlessness and a systolic murmur. (2) *The Abdominal type*, characterized by vomiting, colic, distress and gastro-intestinal crisis, which on occasion has led to an operation for appendicitis. (3) *The Febrile type*, which is characterized by periodic attacks of unexplained fever and chills with or without mild jaundice. (4) *The Anemic type* which is characterized by sudden fever, severe tachycardia, extreme prostration, splenic enlargement, systolic murmur and severe anemia.

The main clinical manifestation of congenital hemolytic anemia are as follows:

(a) *Jaundice*—rarely occurs until school age, then it is distinct but not intense and bears no constant relationship to the rate of blood destruction. The amount of bilirubin in the blood depends not only on the grade of hemolysis but also on the excretory capacity of the liver cells. The jaundice is not associated with itching of the skin, with clay-colored stools, or with the presence of bile pigments in the urine. The jaundice may further be distinguished from that of biliary obstruction in that the greenish tinge so characteristic of the latter is never seen, the color being distinctly yellow.

(b) *Anemia*—is usually moderate but may be marked. The average red cell count is about 4,000,000 with proportionate reduction in hemoglobin, the color and volume index remaining normal or slightly increased. The most distinctive feature is microcytosis, but there is anisocytosis, and poikilocytosis. The red cells are spherical in shape rather than disk-shaped. Spherocytic cells begin to hemolyse at 0.75% NaCL and end the process at 0.4%, while normal cells begin at 0.45% and end at 0.3%.

(c) *Splenomegaly*—is usually the first striking feature of the disease. The size of the spleen and the degree of abdominal discomfort increase during crises, and in some cases may be manifest only at these times.

Rarely is the spleen not palpable at any time during the course of the disease. It usually retains a smooth surface, often indurated, but painless on palpation. The liver on the other hand is normal or is only slightly enlarged.

(d) *Adenopathy*—may occur as a result of local metaplasia, i.e., transformation of lymphoid into myeloid tissue, in the absence of local infection in the anemic child. The glands are usually small, hard, smooth, painless, and localized in the carotid, axillary, or other regions.

(e) *Skeletal Changes*—consist of a considerable thickening of the cranial wall, giving the skull a brush-like appearance similar to that observed in Mediterranean anemia. It is a consequence of overactive bone-marrow, leading to bone hypertrophy, and of excessive irrigation of the bone with blood, causing premature symphysis of the cranial sutures.

(f) *Infantilism*—is often associated with splenomegaly, since the spleen has an inhibitory influence on development. There may also be deformities of the ears, eyes, jaws, fingers, muscles and viscera.

Therapeutic procedures are best described under the headings of general and specific measures.

(a) *General Measures*—The child is put to bed for the entire period of the hemolytic crisis in order to favor return of the latent phase of the disease. During the acute stage of an attack, symptoms are treated as they arise in order to make the child more comfortable. A liquid diet suffices for the immediate needs, additional fluid requirement being fulfilled by parenteral administration if necessary. Transfusions are indicated to ameliorate the symptoms and as a preoperative measure. Fatal anuria from unwarranted transfusions may occur during clinical exacerbations of the disease. Liver is not indicated since parenteral injections may aggravate the hemolytic reaction. Iron is unnecessary because of its efficient conservation by the body. As the acute crisis subsides, anemia is combatted by the administration of ferrous salts, but liver is not well borne. Stimulating therapy is obviously misplaced, for the bone-marrow is already working at full capacity.

(b) *Specific Treatment*—

(1) *Splenectomy*—is invariably followed by prompt and permanent relief of symptoms, because of the removal of the most important blood-destroying organ. The operation is usually performed after the child is restored to remission from the acute crisis, except in extreme cases where immediate removal is necessary to save a child's life. In view of the specificity of splenectomy, the only question to be decided is whether the child has a fair chance to continue without danger of recurrent hemoclastic crises. If the attacks are mild and characterized by slight jaundice, reticulocytosis and anemia, and the child recovers within a few days without

disturbance to his well-being, operation is unnecessary. But if the attacks are severe, associated with marked output of reticulocytes by the bone-marrow, the level of compensation may be entirely too high for the child to maintain over long spans of time—hence the need for splenectomy.

(2) *Radiation Therapy*—this, the use of X-ray, may be used to bring about the destruction of the splenic tissue and is a possible substitute for splenectomy. The procedure is slow and at times is uncertain, although favorable results are often obtained by graded deep therapy in children who are poor surgical risks.

(3) *Splenic ligation*—ligation of the splenic artery has proved successful in cases of short pedicle or diffuse adhesions.

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BILATERAL RENAL CALCULI

Case Report No. 82

Dr. Robert Sullivan D. A. 46—9948

This 7 year old white boy entered the hospital on the 31st of October, 1946 because of abdominal pain of 4 days duration. The pain was gradual in onset and was dull and constant and located in the left upper quadrant. There had been mild dysuria during the two days preceeding admission and one episode of nausea and vomiting on the day of admission an hour and a half after eating. He had also had a mild epistaxis on the day of admission. Throughout this time he was not feverish. His bowels moved normally daily. Since last spring when he had the measles his appetite has been poor and he has lost a few pounds of weight.

He was circumcised as an infant and had one mild bout of diarrhea at eight months. When 4 years old, he had pertussis and last spring he had mumps and measles. Two years ago his mother noticed a "pinkish" color to the urine which has recurred two or three times since then. He has also had since then a few episodes of vague abdominal pain which were relieved by vomiting but not apparently associated with the hematuria. There has been no nocturia.

The parents and two male siblings, ten and four years old, are well. There was no tuberculosis, rheumatic fever, or kidney disease in the family but the ten year old brother had also passed "pinkish" urine several times without other signs of disease.

Physical examination of this child when admitted showed him to be thin, well developed, placid, quite comfortable and not apparently ill though slightly pale. The eyes, including a fundoscopic, the ears, nose and throat were negative except for a mild enlargement of the tonsils with slight reddening of the anterior faucial pillars. The blood pressure was 105/78 and the heart rate 78. There was a transient grade I apical systolic mitral murmur which was considered functional. The abdomen was flat with no involuntary rigidity on light pressure. In the left upper quadrant deep pressure elicited a moderate amount of tenderness and guarding. On the posterior abdominal wall a questionable mass was felt which was considered to be a normal sized left kidney. There was no rebound tenderness and peristalsis was normal. On the left, Murphy's sign was positive. Questioning the child about the location of his abdominal pain revealed that it was usually in the left upper quadrant and sometimes also in the end of his penis.

Examination of the blood showed 11.5 grams of hemoglobin, 7,300

leucocytes, and a normal differential count. Four urine specimens were clear, acid, varied from 1.010 to 1.019 in specific gravity, contained 5 to 10 mgms. % of albumin and showed red blood cells in every microscopic examination—about 6 per high power field. White blood cells in the sediment varied from absent to about 6 per high power field. Casts were absent. No crystals were reported.

During four days of observation he remained afebrile, ate well, had normal bowel movements, vomited once and complained only of tenderness in the left upper quadrant of which he was not conscious when not being examined. A flat plate of the abdomen and an intravenous pyelogram were ordered for the following day but that evening he had severe, steady, sharp pain in the left lower quadrant with nausea and vomiting. Abdominal muscular rigidity was not marked and rebound tenderness was absent. The pain was not controlled by codeine gr. $\frac{1}{2}$ every 4 hours. About midnight he complained of pain in the scrotum and penis, both of which were objectively normal. He urinated small amounts at short intervals. The next morning severe pain was localized in the end of the penis and a dark stone was visible at the meatus. Morphine gr. $\frac{1}{8}$ was administered and removal of the stone was attempted unsuccessfully. He was taken to the operating room, anesthetized, and after meatotomy a hard dark brown stone measuring 13 x 9 x 6 mm. was removed. On its surface were about 20 rather sharp spicules. Since this episode the boy has remained comfortable.

The urinalysis following removal of the stone revealed no essential change since the previous examinations of the sediment and culture of the catheterized specimen was reported as showing no growth. The serum calcium was 12.5 mgm. % and the serum phosphorus 5.1 mgm. %.

In view of the absence of any evident infection in the kidney efforts are being made to rule out hyperparathyroidism as the possible etiologic background for the appearance of the stones. X-rays of the long bones and lateral x-ray of the skull were negative. Examination of the abdomen by means of a flat plate revealed the presence of a large single calculus in the upper pole of the left kidney and 5 or 6 smaller calculi in the superior and middle calices on the right. Due to the presence of the calculi and probably the associated spasm the remaining portions of the upper GU tract were not satisfactorily visualized. However, the bladder showed dye at the end of 4 minutes indicating good function and at the end of 30 minutes showed the bladder to be normal in size, shape and position. From the consideration of the stone that was passed it is considered to be a calcium oxalate stone both on the basis of its color and roentgenologic density.

Interval note: The patient was seen in the follow-up clinic on the 15th of November and was asymptomatic except for a mild bronchitis. The

laboratory work done at that time included a urinalysis which was clear, acid and had a specific gravity of 1.010 and the albumin, sugar and microscopic were all negative. On the same day an estimation of serum phosphatase was 2.7 mgms. per 100 cc. and serum calcium was 11 mgms. per 100 cc. The acid phosphatase was 1.67 King-Armstrong units and the alkaline phosphatase was 6 King-Armstrong units. The Sulkowitch test on the

D. A.: Flat Plate of the Abdomen Indicating the Presence of Several Small Stones on the Right and One Large Calculus on the Left. These Were Calcium Oxalate Stones

10th of November was slightly turbid which was interpreted as normal. On the 15th of November the same test was negative. The parents moved away from Washington after this last visit.

Discussion

Dr. Frederic G. Burke: Urinary calculi have been classified as primary and secondary according to their architecture. Primary stones form as

a pure crystalline precipitate in sterile urine. Primary stones show a radially striated rather than a laminated structure that characterizes the secondary type of stone. Primary stones are the most commonly found in infancy and are usually associated with sterile urine whereas secondary stones more frequently occur in infected urine. According to Campbell, stones may also be classified as being hard or soft, hard stones possessing a definite nucleus and uric acid and calcium oxalate stones being the common examples of this variety. Soft stones, on the other hand, are best exemplified by phosphatic stones and frequently can be crumpled between the fingers when freshly removed from the body. This child presented a rather typical clinical picture of urinary stone in older children which closely simulates that seen in adults. However, many do not show such classic pictures which results in prolonged treatment in some cases for chronic pyelitis or chronic glomerulonephritis.

The incidence of urinary calculi has been variously stated. In this hospital this case represents the third that has been observed in 3 years which incidence would make this diagnosis very rare indeed. Campbell reports the incidence of stones under 15 years of age to be approximately 0.3%. The great majority of stones in children occur before the tenth birthday and they have been reported in the newborn. There is a definite sex predominance and occurs most frequently in males possibly due to the higher incidence of infra-vesicle obstruction in young males. Familial tendency which has been reported by many authors is probably negligible except in cases of cystine disease which is known to be an hereditary diathesis. In hot dry climates where there is considerable skin evaporation and urinary concentration the incidence of stone is reported to be much higher than in the temperate climates. Dietary factors play an important role in the incidence of stone in many parts of the world.

Anomalous organs are more prone to stone formation than are normal organs and urinary stasis and infection are the usual demonstrable factors in stone formation. Disturbance of crystalloid-colloid equilibrium caused by marked increased in colloids of inflammatory origin also play an important role. An excess of crystalloid precursors in the diet does not seem to influence materially the incidence of urinary stone.

The normal calcium and phosphorus ratio noted in this case tends to rule against a disturbance of the parathyroid gland as the etiologic agent in the formation of this child's stones although calcium studies should be followed through to confirm or disaffirm this one laboratory procedure. The nature of the stone passed would indicate that it is of an oxalate nature which type are second only to uric acid stones both in adults and in the young. Furthermore, the presence of spicules which tend to cling to the mucosa causing considerable spasm during their migration is characteristic of calcium oxalate stones.

The treatment of the case under discussion will have to be determined by the course he follows. Since one relatively large stone has been passed, it is possible that others will be similarly discharged from their position in the kidney. At the present time they do not seem amenable to surgery. Statistical data concerning the recurrence of renal stone in children is inadequate but it is believed that the incidence is about 10%.

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ASTHMA: REPORT OF A FATAL CASE

Case Report No. 83

Dr. Clifford J. Tichenor M. H. 46-8824

A 3 year old colored female was brought to the hospital in October because of respiratory distress with wheezing of nine hours duration.

Except for two brief asthmatic attacks two months prior to admission, this child had been ostensibly well. No history of infection preceding the present attack was elicited. There had been no exposure to cold, inhalation of cold air, smoke or irritating gases, and no psychic factors could be indicated to account for this attack. Feather pillows and cotton mattresses were not used in the patient's household.

The past history was negative for eczema, other skin rashes, food sensitivities, hay fever, conjunctivitis, and inhalation atopies. Immunization against diphtheria, whooping cough and smallpox had been accomplished without untoward effects at one year of age. No animal pets were kept at home. The possibility of ingestion of any foreign body was denied. The family history was negative for any conditions simulating the disease of the patient.

The present illness began suddenly the morning of the day of admission with a simple wheezing which became rapidly and progressively more severe, so that within a few hours the child was having difficulty breathing and had vomited several times. No relief was obtained when the family physician gave an unknown amount of epinephrine by injection.

Physical examination at the time of admission revealed a fairly well developed, undernourished colored female child, appearing critically ill and anxious, restless but exhausted, moderately cyanotic, using all her accessory muscles of respiration but in spite of this appearing air hungry. The thoracic excursions were rapid and very shallow, the chest seeming to remain in the position of inspiration. Marked supra-sternal tugging was noted and abdominal breathing was a prominent feature. The pharynx did not appear inflamed or edematous.

Percussion of the thorax showed a moderate hyper-resonance bilaterally and numerous sibilant and musical rales obscuring the breath sounds were heard on auscultation. The heart action was rapid and weak. No mediastinal shift could be determined. The temperature was 101.8°, the pulse 130 and the respirations 50.

The patient was immediately placed in an oxygen tent, given 4 minims of adrenalin subcutaneously and closely observed. There being no relief of dyspnea noted, 1 cc. of adrenalin in oil was administered intramuscu-

larly, and shortly followed by 1.5 grains of phenobartital to relieve apprehension and restlessness. Additional subsequent therapy included one half a tablet of tedral orally and this was repeated twice in the subsequent 8 hours. The oxygen tent was discontinued and a croup tent substituted. One dram of benadryl was also given orally and twice repeated. An additional 0.75 grains of phenobarbital was given hypodermically.

Despite this therapy the temperature rose to 103.4°, the pulse to 195 and the respirations to 68. Air hunger became more severe, pronounced cyanosis supervened and the course was rapidly downhill, the patient expiring from asphyxia 15 hours after admission.

The only laboratory data obtained was a growth of hemolytic staphylococcus aureus in the throat culture.

The pathological diagnoses at necropsy included:

1. Asphyxia, due to generalized bronchial obstruction from excess bronchial mucus.
2. Pulmonary emphysema.
3. Right heart failure, as evidenced by dilatation of the right heart and marked engorgement of the great veins.

Microscopic section of the lungs revealed emphysema and pulmonary congestion and some infiltration with round cells and thickening of the alveolar walls. Culture of the cisternal fluid and hearts blood showed no growth, but culture of the lungs and bronchi grew out gram positive diplococci having the morphology of pneumococci but pneumo-typing was unsatisfactory. Non-hemolytic staphylococcus aureus was also present.

Discussion

Benjamin P. Lafsky, M.D.: The case under discussion is probably caused by an overwhelming infection in an allergic child. The type of infection is undetermined but the possibility of virus etiology should be kept in mind principally as a factor in differential diagnosis if a similar case occurs in the future. The reasons for believing the case is one of overwhelming infection are the rapid course and fatal termination, presence of fever, dyspnea not solely in expiration but of the inspiratory and expiratory type, no relief from epinephrine and absence of eosinophiles in microscopic sections of lung.

Since this case was initially thought to be asthma and treated as such it might be well to describe the treatment of asthma in children from a practical aspect.

In asthma as in any other disease the etiology must be sought in order to eliminate the cause and thus give the patient relief. Etiology can be considered under the following headings:

1. Inhalants
2. Ingestants
3. Infection
4. Psychogenic factors
5. Physical agents and non-specific causes

A careful history, a complete physical examination, certain laboratory examinations and x-rays greatly aid in finding the cause or causes particularly if one thinks of allergic factors as well as what prescription or medicinal therapy to prescribe. In the history remember the seasonal occurrence of pollen asthma; trees in the spring from March to June; grasses and plantain in the summer from May through July; and ragweed in the fall from the middle of August to the end of September. Sometimes the removal of a pillow or rug, a change of environment, moving to a different climate, getting rid of a cat or dog or eliminating some food from the diet will give prompt relief from asthma but generally a great deal of time and effort is required to get at the cause. Skin tests are very helpful but not absolutely diagnostic of allergic factors. They are more important with the inhalants than the foods. The possibility of a combination of factors should always be kept in mind as the child may be sensitive to foods and inhalants, have a focus of infection in the sinuses or bronchi as well as a psychogenic element to his asthma. Furthermore, clinical sensitivity may change from year to year necessitating a reevaluation and retesting when asthmatic symptoms recur in a patient who has previously been under control.

Inhalants: The principle offenders are house dust, pollens, animal danders, orris root and cottonseed. Removal of sources of inhalants from the environment, covering pillows, mattresses and furniture with impermeable casings, and injections of inhalant and extracts give good results if inhalants are the only cause. Air conditioning and window filters are of value in inhalant allergy particularly that due to pollens.

Foods: These are quite important in infants and children, therefore the causative foods should be sought for by skin tests, trial diets and the food diary. The diagnosis and elimination of food allergy is very difficult and requires a great deal of experience and patience but can be accomplished by any physician if he is willing to take the time. Knowing that the chief offenders are milk, eggs, wheat, corn, other cereal grains, peas, beans, nuts, fish, chocolate and oranges, one can prescribe a basic limited diet of a substitute for cows milk such as soy bean milk, protein hydrolysate or goats milk or one of these milks plus rice, lamb, carrots, beets, squash and pears provided none of these have given positive skin tests. Vitamin C and drisdol may be added. If no results are obtained and foods are still suspected another diet can be tried. If relief occurs on the trial diet, foods

may be added at 4 day intervals and the effect watched. Add foods such as bread, milk, fruits, vegetables, meats, foods containing eggs, then egg itself depending on the age of the child and the results of the skin tests and history. Naturally if no relief occurs with the basic trial diet, it is useless to go on with single additions of foods. An accurate diary in a notebook should be kept of all foods eaten and the symptoms as they occur in order to evaluate results of the diet.

Infection in the sinuses, pharyngeal lymphoid tissue and bronchi in particular should be sought, although foci of infection are not as frequent in children as in adults. Tonsillectomy is seldom of benefit in asthma and should be done only if it is necessary for the general health of the child. In fact, tonsillectomy is often followed by the onset of asthma in an allergic child. Sinusitis if found should be treated conservatively as surgery is rarely necessary. At Johns Hopkins Hospital, radium therapy has been introduced and developed for eliminating masses of infected lymphoid tissue in the posterior pharynx and nasopharynx with apparently good results.

Psychogenic Factors: Keep these in mind as they may be an additional or, as some maintain, the sole cause of asthma. The cases usually fall in the following categories according to Dr. Hyman Miller:

1. Trying to obtain sympathy or affection. Illness gets the child more attention and affection. A new baby gets all the attention so the older child has asthma to get his share.
2. Expressing aggression or hostility. Parents may pick on a child too much constantly correcting him or parents may act as if the child is a burden thus causing hostile or aggressive actions in the child.
3. Hiding shameful emotions. Child may dislike one of parents but suppresses this undesirable emotion.

Physical agents and non-specific factors: These are important at times and comprise overexertion, crying, fatigue, chilling, change of weather, heat or cold all of which may precipitate an attack.

Drug Therapy

"Asthmatic bronchitis", allergic cough and slight attacks of asthma: The drugs of greatest value in this category are ephedrine, iodides, aminophylline, codeine sulphate, phenobarbital, benadryl and pyribenzamine.

Ephedrine sulfate or hydrochloride may be prescribed alone in doses of $\frac{1}{8}$ grain for a child under 1 year, $\frac{1}{4}$ grain from 1 to 10 years and $\frac{3}{8}$ grain for older children. The dose may be repeated 4 times in 24 hours. It may be given in the 3% aqueous solution in drop dosage from 5 to 15 drops, each drop representing about $\frac{1}{30}$ grain. The syrup of ephedrine sulphate or hydrochloride containing 2 grains to the ounce is very convenient and may be prescribed in $\frac{1}{2}$ to one teaspoon doses. Ephedrine sulphate or

hydrochloride is also obtainable in tablets of $\frac{1}{4}$ grain or capsules of $\frac{3}{8}$ or $\frac{3}{4}$ grain.

Phenobarbital gr. $\frac{1}{8}$ to $\frac{1}{4}$ is useful in suppressing the nervousness and insomnia caused by ephedrine in some patients.

The iodides are of value in relieving asthma by liquefying sputum and sometimes will control slight asthma by itself. It is of value as a harmless but effective remedy in chronic asthmatics and should be used freely except in those who are sensitive to it. The saturated solution of potassium iodide 3 to 10 drops three times a day in water, milk or fruit juices may be tried or syrup of hydriotic acid 10 drops to 1 teaspoon three times a day.

Aminophylline grain I to grain III three times a day sometimes is of value or grains III in a suppository at bedtime.

Benadryl in elixir which contains 10 mgm. per dram or in capsules containing 25 or 50 mgm. may be given 3 or 4 times daily or only when necessary particularly at night because of its sedative effect. It is effective in slight asthma but is of very little benefit in severe cases. Pyribenzamine is also benificial in slight asthma in doses of 25 to 50 mgm., i.e. $\frac{1}{2}$ to 1 tablet one to four times daily. Recently pyribenzamine has been found to give relief in a nebulizer but the details have not been worked out. Benadryl or pyribenzamine combined with ephedrine is better than either alone.

The following prescriptions are of value in this category of patients.

℞

Codeine sulphate (or phenobarbital sod.)	gr. IV to VI
Potassium iodide	dr. I to dr. II
Syr. ephedrine hydrochloride (Gr. II to oz.)	q.s. oz. IV

Sig. $\frac{1}{2}$ to 1 teasp. q 5 h p.r.n. for cough or asthma

℞

Codeine sulphate	gr. IV to VI
Ephedrine sulphate	gr. IV to VI
Potassium iodide	dr. I to dr. II
Elixir phenobarbital	oz. II
Syrup simplex	q.s. oz. IV

Sig. $\frac{1}{2}$ to 1 teasp. q 5 h p.r.n. for cough or asthma

℞

Ephedrine sulphate	gr. IV to gr. VI
Potassium iodide	dr. I to dr. II
Elixir benadryl	q.s. oz. IV

Sig. $\frac{1}{2}$ to 1 teasp. q 5 h p.r.n. for cough or asthma

Ephedrine salts and potassium iodide are compatible with elixir of benadryl but codeine sulphate apparently does not make a good solution; however ethylmorphine HCl does. It is not desirable to use sedatives or narocotics with benadryl because of its own sedative effect.

℞

Ephedrine sulphate..... gr. $\frac{1}{6}$ to $\frac{3}{8}$
Aminophylline..... gr. I to III
Phenobarbital..... gr. $\frac{1}{8}$ to $\frac{1}{2}$
Sig. one such caps q 4 h p.r.n. for asthma.

Another good capsule is:

℞

Papaverine HCl..... gr. $\frac{1}{4}$ to $\frac{1}{2}$
Ephedrine sulphate..... gr. $\frac{1}{6}$ to $\frac{3}{8}$
Aminophylline..... gr. I to III
Phenobarbital..... gr. $\frac{1}{8}$ to $\frac{1}{4}$
Sig. one caps q 4 h p.r.n. for asthma.

Belladonna or atropine is sometimes of value in combination with ephedrine and iodides but dries out bronchial secretions.

There are many propietary mixtures on the market most of which are needlessly complex. However, some patients tolerate synthetic ephedrine as contained in "Franol" tablets or neosynephrine as in "adenophrine" capsules better than ephedrine salts. The propietaries may therefore be useful at times.

Epinephrine HCl 1–1000 may be given hypodermically for temporary relief or for its diagnostic value but is usually not necessary in slight asthma or allergic cough.

Moderate asthma: When treating a moderate attack of asthma it is best to give a small dose of epinephrine HCl 1-1000 hypodermically for its prompt but temporary relief but the dosage is of greatest importance in children as usually too much is given causing undesirable side reactions as nervousness, trembling, pallor, faintness and nausea. A tuberculin type syringe is preferable to the usual hypodermic syringe since the dosage is easier to measure, more accurate and the tendency to overdose is less likely. The dose under 2 years is 0.1 cc. and in older children 0.2 cc. is sufficient. It is best to repeat the dose in 15 to 30 minutes in order to prolong the effect. Adrenalin in peanut oil $\frac{1}{4}$ to $\frac{1}{2}$ cc. may be given intramuscularly remembering that the child may be sensitive to peanuts. Occasionally 2 or 3 drops of epinephrine HCl 1-1000 under the tongue will give relief and may be tried. In older children who have taken a great deal of epinephrine a dose of $\frac{1}{2}$ cc. may be well tolerated but usually this is too much for the initial or occasional dose.

Epinephrine HCl 1-1000 solution in a special hand nebulizer may be inhaled by mouth in selected cases. Only one to three deep breaths should be inhaled but the dangers of overdosage should be explained to the parents and too frequent use should be discouraged.

Aminophylline, ephedrine, iodides, sedatives, benadryl and pyribenzamine should be used in between doses of epinephrine which may be repeated several times a day until the attack is over after which you can try to find the cause.

Severe asthma and Status Asthmaticus: The previous treatment is usually sufficient for an occasional attack or one which responds in a few days to treatment. However, if the asthma persists and the patient is confined to the home or becomes bedridden, other measures become necessary. Intractable asthma usually means constant severe asthma which still responds to epinephrine. Status asthmaticus is a constant severe, prostrating asthma which has ceased to respond to epinephrine. Fortunately the latter is rare in children as is death from asthma.

These patients are preferably treated in the hospital. They have usually had plenty of epinephrine, ephedrine, aminophylline and sedatives. Oxygen or helium 80% and oxygen 20% by nasal catheter, pressure mask or tent may give considerable relief of anoxia. However, these gases tend to dry out the bronchial secretions and the low temperature of a tent is not good for an asthmatic. Watch the patient and discontinue or change the oxygen therapy if no benefit is noted.

Dr. Barach of New York recommends the inhalation of a mixture of equal parts of 1% epinephrine (1-100) and 1% neosynephrine which is nebulized by the stream of oxygen or helium and oxygen. The dose in adults is 0.5 cc. of each; therefore in a child 0.2 cc. of each could be tried. Aminophylline in aerosol frequently gives a great deal of relief. Penicillin or sulfacetamide could be nebulized and inhaled during oxygen treatment also. Sodium sulfadiazine has been found too alkaline for inhalation.

If dehydration or peripheral circulatory collapse is present, 5% glucose in distilled water may be given intravenously in the usual dosage of 10 cc. per pound. If the patient is not dehydrated, 20-50 cc. of 25% glucose intravenously sometimes will give relief. Epinephrine in a dosage of 0.1 to 0.3 cc. or aminophylline gr. 2 to 3 may be added to the glucose solution. Epinephrine sometimes works intravenously when it has ceased to benefit hypodermically but small doses should be tried.

Satured solution of potassium iodide 5 to 10 drops three times a day is of value for its expectorant action. If there is vomiting it may be given per rectum in larger doses. It may be given intravenously but it is usually well absorbed from the mouth or rectum and the patient might be sensitive to iodides.

A dust and inhalant free room may be helpful as is air conditioning or a window filter. Omit foods to which the patient is allergic or a basic elimination diet may be tried.

The child should be supported and relieved as much as possible without

resorting to narcotics or too many sedatives until the response to epinephrine is again obtained. Narcotics are especially dangerous in children as the suppression of respiration may be enough to cause a fatality. However, phenobarbital or sodium phenobarbital, ether in oil per rectum ($\frac{1}{2}$ to 1 oz. of ether in equal quantity of olive oil) or paraldehyde in mineral oil per rectum are useful in giving some rest. Ether anesthesia by inhalation is occasionally tried and bronchoscopic aspiration will sometimes give prompt relief. Both of these measures are used together at times.